Original Article

Patients with a Hypertensive Response to Exercise Have Impaired Left Ventricular Diastolic Function

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An exaggerated increase in systolic blood pressure prolongs myocardial relaxation and increases left ventricular (LV) chamber stiffness, resulting in an increase in LV filling pressure. We hypothesize that patients with a marked hypertensive response to exercise (HRE) have LV diastolic dysfunction leading to exercise intolerance, even in the absence of resting hypertension. We recruited 129 subjects (age 63±9 years, 64% male) with a preserved ejection fraction and a negative stress test. HRE was evaluated at the end of a 6-min exercise test using the modified Bruce protocol. Patients were categorized into three groups: a group without HRE and without resting hypertension (control group; *n*=30), a group with HRE but without resting hypertension (HRE group; *n*=25), and a group with both HRE and resting hypertension (HTN group; *n*=74). Conventional Doppler and tissue Doppler imaging were performed at rest. After 6-min exercise tests, systolic blood pressure increased in the HRE and HTN groups, compared with the control group (226±17 mmHg, 226±17 mmHg, and 180±15 mmHg, respectively, $p<0.001$). There were no significant differences in LV ejection fraction, LV end-diastolic diameter, and early mitral inflow velocity among the three groups. However, early diastolic mitral annular velocity (E′) was significantly lower and the ratio of early diastolic mitral inflow velocity (E) to E′ (E/E′) was significantly higher in patients of the HRE and HTN groups compared to controls (E′: 5.9±1.6 cm/s, 5.9±1.7 cm/s, 8.0±1.9 cm/s, respectively, $p<0.05$). In conclusion, irrespective of the presence of resting hypertension, patients with hypertensive response to exercise had impaired LV longitudinal diastolic function and exercise intolerance. (*Hypertens Res* 2008; 31: 257–263)

***Key Words*: hypertension, diastolic function, exercise**

Introduction

Hypertension exerts a deleterious effect on ventricular function by causing both structural and functional changes in the heart (*1–3*). Increase in systolic blood pressure (SBP) causes slow myocardial relaxation, left ventricular (LV) hypertrophy and potentially adverse effects on passive chamber stiffness (*4*, *5*). Thus, many patients with long-standing hypertension have Doppler echocardiographic evidence of impaired diastolic function, which may limit exercise tolerance.

Arterial SBP normally increases during exercise in both patients with hypertension and subjects without hypertension (*6*, *7*). The increase in arterial SBP during exercise is frequently exaggerated, especially in subjects over 60 years and patients with hypertension (*8*, *9*). The increase in arterial pressure during exercise has been shown to increase LV afterload, thus slowing LV relaxation and reducing early filling (*4*). The

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Table 1. Clinical Characteristics of Study Population (n=129)

	Control	HRE	HTN
Number (%: male)	30 (57)	25 (72)	74 (65)
Age (years)	60±7	65±7	64±10
Body mass index (kg/m^2)	22.3±2.9	23.6±3.8	24.3±2.8*
Resting systolic BP (mmHg)	123±11	126±9	162±14*,†
Resting diastolic BP (mmHg)	73±7	75±9	89±13*,†
Resting HR (beats/min)	76±16	84±16	81±15
Diabetes mellitus (n (%))	5 (18)	7 (28)	28 (38)
Hyperlipidemia (n (%))	8 (29)	9 (36)	41 (56)*
Anemia (n (%))	4 (18)	5 (22)	16 (24)
Renal dysfunction (n (%))	4/23 (17)	2/23 (9)	9/65 (14)

Data are expressed as mean±SD or n (%). *$p<0.05$ *vs*. control. †$p<0.05$ *vs*. HRE. HRE, hypertensive response to exercise without resting hypertension; HTN, hypertensive response to exercise with resting hypertension; BP, blood pressure; HR, heart rate.

ventricle operates at higher volumes (utilization of preload) and there is an increase in left atrial pressure in response to increased systolic load. Thus, a marked increase in SBP during exercise causes an increase in left atrial pressure, leading to exercise intolerance (*10*). However, there is limited evidence as to whether patients with hypertensive responses to exercise, and without resting hypertension, have diastolic dysfunction and exercise intolerance.

In the present study, therefore, we examined LV diastolic performance using two-dimensional (2-D), pulsed Doppler and spectral tissue Doppler echocardiography as well as exercise tolerance in patients with a hypertensive response to exercise but no resting hypertension.

Methods

Patient Selection

We recruited 129 subjects from among patients undergoing exercise testing for coronary artery disease at our institution. Selection criteria included left ventricular ejection fraction >50% by 2-D echocardiography, no evidence of myocardial ischemia on treadmill exercise testing, and no valvular heart disease. Ambulatory blood pressure was measured in all patients, and patients with white-coat hypertension and white-coat normotension were excluded (*11*). Patients with other diseases that could limit exercise tolerance (*i.e.*, emphysema, severe renal dysfunction, and severe liver dysfunction) were excluded.

Protocol

Each subject provided informed, written consent to the protocol, which was approved by our institutional review board. All baseline medications were discontinued on the day of the study. Resting 2-D echocardiogram and tissue Doppler measurements were obtained. The subjects then underwent a graded symptom-limited maximum treadmill exercise test using the modified Bruce protocol. Electrocardiography, heart rate (HR), and SBP and diastolic blood pressure (DBP) measurements were obtained using an automated sphygmomanometer and were monitored every minute throughout the study. The estimated workload was determined in metabolic equivalents (METs), which were calculated from a previously validated formula:

$$\text{METs} = \text{VO}_{2\ \max}/3.5,$$

$$\text{VO}_{2\ \max} = 6.7 - 2.82 \times [\text{weighting factor for gender}] + 0.056 \times [\text{duration of treadmill test in s}],$$

where the weighting factor is 1 for men and 2 for women (*12*, *13*). The increase in SBP normalized for exercise capacity (index of SBP increase) was calculated as the difference between peak SBP during exercise and resting SBP divided by METs (ΔSBP/METs) (*14*).

Study Subjects

A hypertensive response to exercise (HRE) was defined as a maximum SBP/DBP ≥210/105 mmHg in males, and ≥190/105 mmHg in females, at the end of a 6-min (7 METs) exercise test using the modified Bruce protocol (*15*, *16*). When patients could not tolerate 6-min exercise, HRE was evaluated at the maximum exercise time. A clinical history of hypertension was defined as an elevated SBP/DBP (≥140 mmHg in SBP and/or ≥90 mmHg in DBP) documented by the referring physician. All patients with resting hypertension showed a hypertensive response to exercise. Therefore, patients were divided into three groups according to their blood pressure in response to exercise in this study (Table 1): a group without HRE and without resting hypertension (control group), a group with HRE but without resting hypertension (HRE group), and a group with both HRE and resting hypertension (HTN group).

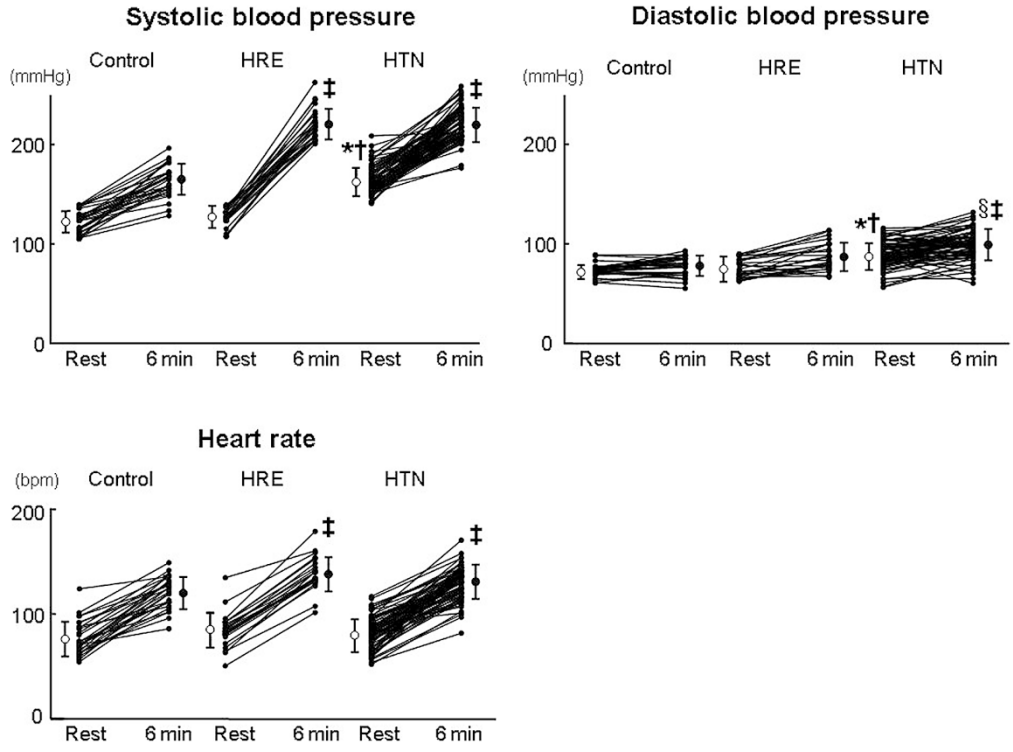

Fig. 1. *Changes in systolic blood pressure, diastolic blood pressure, and heart rate at rest and at 6-min after the start of exercise in the control group, the HRE group (hypertensive response to exercise without resting hypertension) and the HTN group (hypertensive response to exercise with resting hypertension).* $^{*}p < 0.05$ *vs. control at rest,* $^{\dagger}p < 0.05$ *vs. HRE at rest,* $^{\ddagger}p < 0.05$ *vs. control after exercise,* $^{\S}p < 0.05$ *vs. HRE after exercise.*

Echocardiographic Measurements

Detailed 2-D, pulsed Doppler and spectral tissue Doppler echocardiography were performed at rest, including on-line analysis of all patients as previously reported (Vivid 7; GE Electronics, Syracuse, USA) (*17*). LV M-mode measurements of wall thickness and end-diastolic and end-systolic diameters were used for calculating LV fractional shortening and LV ejection fraction. Patients with LV hypertrophy, defined as a septal or posterior wall thickness >12 mm, were excluded from this study (*18*). Early (E) and late (A) transmitral flow velocity and its deceleration time were measured by pulsed-wave Doppler from the apical four-chamber view, and medial mitral annular diastolic velocities were measured with tissue Doppler imaging. The medial mitral annular peak systolic velocity, and early (E′) and late (A′) diastolic velocities were determined by spectral tissue Doppler imaging at the medial corner of the mitral annulus from the apical four-chamber view using standard methods. The mitral annular peak systolic velocity reflects longitudinal LV systolic function (*19*). The E′ velocity is relatively independent of preload and inversely related to the time constant of isovolumic relaxation (*20*). The ratio of E to E′ (E/E′) reflected LV filling pressures (*20*, *21*).

Statistical Analysis

Continuous variables are presented as the mean values±SD. Group differences were compared using analysis of variance (ANOVA); post-hoc multiple group comparisons were assessed with the Bonferroni method, adjusting for three-way comparisons. Linear regression was used to determine correlations between continuous variables. Data were analyzed using standard statistical software (SPSS version 11.5; Chicago, USA). A p value of <0.05 was considered significant.

Results

Clinical Characteristics

A total of 129 patients were divided into control ($n=30$), HRE ($n=25$), and HTN groups ($n=74$). There was no difference in age among the three groups. At baseline, body mass index and incidences of hyperlipidemia were higher in the HTN group compared to the control group (Table 1). Other baseline characteristics, including gender, incidence of anemia (defined as a hemoglobin concentration <13.0 g/dL in men and <12.0 g/dL in women) (*22*), and renal dysfunction (defined as an estimated glomerular filtration rate [eGFR] <60 mL/min as calculated by the Modification of Diet in

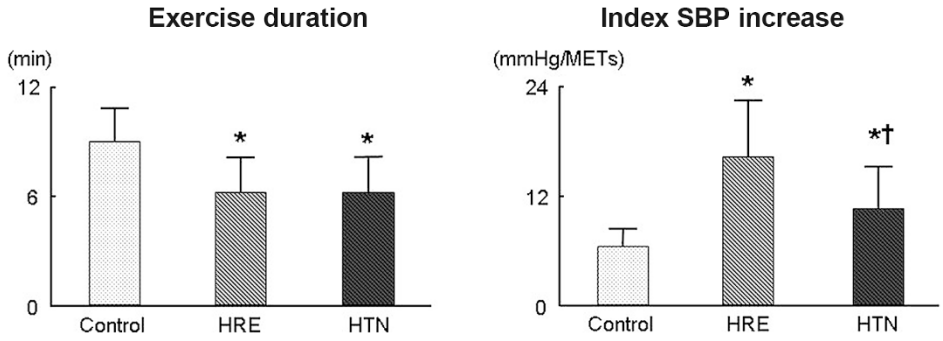

Fig. 2. *Differences in exercise duration and the systolic blood pressure (SBP) index in the control group, the HRE group (hypertensive response to exercise without resting hypertension) and the HTN group (hypertensive response to exercise with resting hypertension). *p < 0.05 vs. control, †p < 0.05 vs. HRE.*

Table 2. Two-Dimensional and Conventional Doppler Echocardiographic Data

	Control	HRE	HTN
LV end diastolic diameter (mm)	45.6±3.3	46.6±5.7	45.9±5.1
LV end systolic diameter (mm)	29.0±3.3	28.6±5.9	27.7±4.5
Septal wall thickness (mm)	8.5±1.5	9.7±2.0*	10.3±1.8*
Posterior wall thickness (mm)	8.7±1.3	9.8±1.6*	10.3±1.5*
Ejection fraction (%)	66±7	69±10	70±7
Left atrial diameter (mm)	33.4±4.0	37.8±6.7*	36.9±4.5*
Mitral E wave (cm/s)	63.4±18.2	61.6±14.6	63.9±15.9
Mitral A wave (cm/s)	63.9±17.3	79.5±18.3*	84.8±19.3*
Mitral E/A	1.00±0.37	0.76±0.22*	0.76±0.24*
E deceleration time (ms)	216±46	219±35	222±43

Data are expressed as mean±SD. *$p<0.05$ *vs*. control. HRE, hypertensive response to exercise without resting hypertension; HTN, hypertensive response to exercise with resting hypertension; LV, left ventricular; Mitral E, early transmitral flow velocity; Mitral A, late transmitral flow velocity.

Renal Disease [MDRD] method) (*23*) were similar among the three groups. Forty-four patients in the HTN group were treated with antihypertensive drugs such as β-blockers ($n=7$), angiotesin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers ($n=26$), calcium channel blockers ($n=25$), and diuretics ($n=1$).

Exercise Electrocardiography

At baseline, resting SBP and DBP were significantly higher in the HTN group than the HRE and control groups. During exercise, SBP and DBP, as well as heart rate, were significantly increased in all three groups (Fig. 1). The rise in SBP was larger in the HRE group than the HTN and control groups, despite the fact that there were no significant differences in the rise in HR. The exercise durations in both the HRE and HTN groups were significantly shorter than that in the control group, while they were similar to each other (control 8.9±1.9 min, HRE 6.2±2.2 min, and HTN 6.2±2.2 min; Fig. 2). The index of SBP increase (ΔSBP/METs) was higher in the HRE group than the HTN or control groups (Fig. 2).

Echocardiography at Rest

The left atrial diameter was longer and the septal and posterior wall thickness, as measured along the parasternal long axis view, were significantly thicker in the HRE and HTN groups than in the control group. There were no significant differences in LV end-diastole and end-systole diameters or the LV ejection fraction among the three groups (Table 2).

For mitral LV inflow measurements (pulsed Doppler echocardiography), the mitral A wave was higher and E/A was lower in the HRE and HTN groups compared to the control group, while there were no significant differences in the mitral E wave and its deceleration time among the three groups (Table 2).

For tissue Doppler imaging, mitral annular peak systolic velocity was impaired in the HRE and HTN groups to compare to the control group (control 7.98±1.36 cm/s, HRE 7.07±1.08 cm/s [$p< 0.05$ *vs*. control], and HTN 7.26±1.06

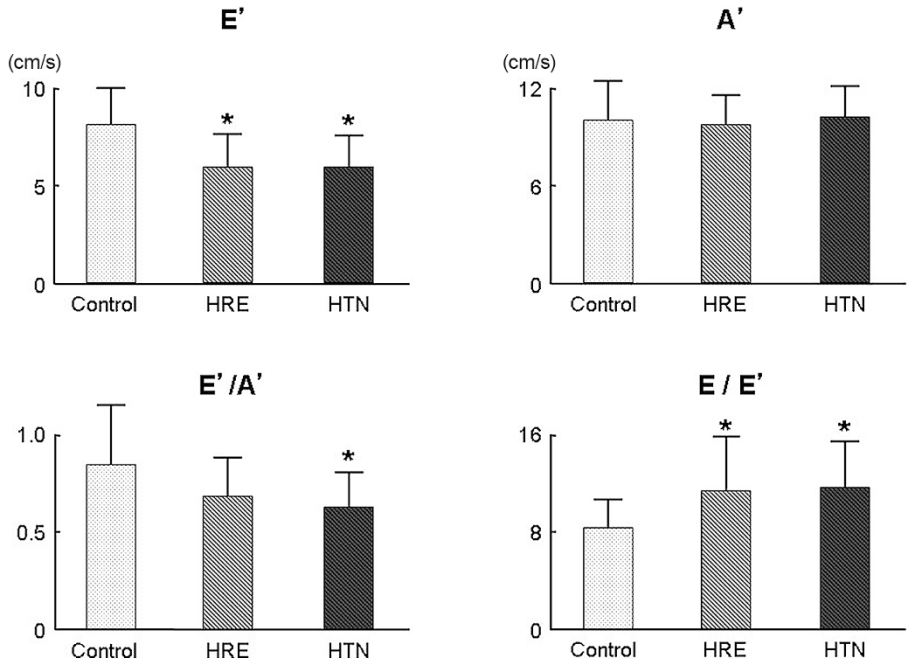

Fig. 3. *Early (E′) and late (A′) diastolic mitral annular velocities were measured, and E/E′ and E′/A′ were calculated in the control group, the HRE group (hypertensive response to exercise without resting hypertension) and the HTN group (hypertensive response to exercise with resting hypertension). *p < 0.05 vs. control.*

cm/s [$p<0.05$ *vs*. control]). E′ was significantly lower and E/E′ was significantly higher in the HRE group as well as the HTN group compared to the control group, while there were no significant differences in E′ and E/E′ between the HRE and HTN groups (Fig. 3).

Discussion

In the present study, we showed that E′ was significantly lower and E/E′ was significantly higher in patients with a hypertensive response to exercise, suggesting an impairment of LV diastolic dysfunction, despite the absence of resting hypertension. LV diastolic dysfunction associated with exercise intolerance in patients with hypertensive response to exercise but no resting hypertension was similar in degree to that of patients with both hypertensive response to exercise and resting hypertension.

Consistent with previous reports, we observed a correlation between arterial hypertension and impaired LV diastolic performance in patients with hypertension (*4*, *5*). In increased systolic arterial pressure, there is an upward shift in the LV diastolic pressure–volume ratio, resulting in an increase in left atrial pressure indicated by an increased E/E′ (*24*), and slow LV relaxation, as indicated by a decreased E′.

Interestingly, our results demonstrated that the patients who exhibited a hypertensive response to exercise even without resting hypertension had impaired longitudinal diastolic function and higher LV filling pressure. Marked systolic hypertension during exercise is common in subjects over the age of 60 years and occurs in many patients with hypertension, even when BP is well controlled at rest (*25–27*). This may be a manifestation of the arterial stiffening that often accompanies diastolic LV dysfunction. A hypertensive response to exercise is associated with an increased incidence of chronic hypertension during follow-up and has been proposed as a preclinical stage of hypertension (*28*, *29*). In contrast with the present results, Mottram *et al*. reported that patients with HRE had similar exercise capacity and diastolic function compared with control subjects (*14*). This difference in findings may have been due to a difference in the time at which HRE was measured. We estimated HRE at 6 min after the start of exercise (*15*), while Mottram *et al*. measure HRE at the maximum exercise intensity in their study. Therefore, the patients assigned to the HRE group in the present work may have had a more aggressive hypertensive response to exercise.

The exercise-induced increase in systolic arterial pressure may be partly mediated by angiotensin II. In the present study, though we did not measure any hemodynamic parameters (including renin, angiotensin, aldosterone, and catecholamine), it may be possible that plasma and tissue levels of angiotensin II were increased during exercise in patients with hypertensive response to exercise and without resting hypertension.

We also showed that the exercise intolerance of patients who exhibited a hypertensive response to exercise was due to LV diastolic dysfunction. In support of this, Little *et al*. found

that diastolic function abnormalities may contribute to exercise intolerance in patients with systolic dysfunction and patients with primary diastolic dysfunction (*30*).

Study Limitations

Several important limitations bear mentioning. First, we recruited subjects for this study from a patient pool undergoing exercise testing because of suspected coronary artery disease. Although the exercise testing was negative, ischemic heart disease cannot be totally ruled out. Therefore, the subjects in our study may not accurately reflect the larger community.

Second, we measured exercise tolerance using the modified Bruce protocol of treadmill exercise. The duration of exercise in our study may have been influenced by the patients' motivation and subjective interpretation of their symptoms during exercise. These confounding variables may have affected our results. Alternatively, the lower SBP during exercise may have influenced the examiner to push the subject further. However, exercise tolerance was significantly higher in control subjects than in patients with a hypertensive response to exercise.

Conclusions

LV diastolic function and exercise tolerance were significantly impaired in patients with a hypertensive response to exercise, even in the absence of resting hypertension. Thus, a marked hypertensive response to exercise may be an important therapeutic target in the future.

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